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14. ABSTRACT
The purpose of the research sup ported by t his award is to conduct a Phase II clinical trial (study) of an adenovirus/PSA (Ad/PSA) vaccine for the treatment of prostate cancer. Two protocols have been used in the trial: #1 - *Phase II study of Adenovirus/PSA vaccine in men with recurrent prostate cancer after local therapy*; and #2 - *Phase II study of Adenovirus/PSA vaccine in men with hormone refractory prostate cancer*. I n the first p rotocol men with n ewly recurre nt prostate cancer were randomized to one of two arms of the study. Patients in Arm A received the Ad/PSA va ccine only; t hree injections spac ed 30 days apart. Patient s in Arm B received androgen deprivation t herapy (ADT) followed at day 14 b y the Ad/PSA vaccine, again with t hree injections. In the second protocol men with hormone refracto ry prostate cancer were injected with the vaccine only, three injections 30 days apart. Patients were followed for toxicity, development of anti-PSA immue responses, and evidence of a clinical effect of the vaccination. The latter includes changes in serum PSA and prostatic acid ph osphatase (PAP) levels and in PSA doubling times (PSADT). Protocol #2 patients also have CT & bone scans to monitor their prostate cancer.

15. SUBJECT TERMS
Prostate cancer; immunotherapy; vaccine

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INTRODUCTION

The purpose of the research supported by this award is to conduct a Phase II clinical trial (Study) of an adenovirus/PSA (Ad/PSA) vaccine for the treatment of prostate cancer. Two protocols are being used in the trial: #1 – *Phase II study of adenovirus/PSA vaccine in men with recurrent prostate cancer after local therapy,* and #2 – *Phase II study of adenovirus/PSA vaccine in men with hormone refractory prostate cancer*. In the first protocol men with recent documentation of recurrent prostate cancer are randomized to one of two arms of the study. Patients in Arm A receive the Ad/PSA vaccine only; three injections spaced 30 days apart. Patients in Arm B will receive androgen deprivation therapy (ADT) followed at day 14 by the first of three Ad/PSA injections. In the second protocol men with hormone refractory prostate cancer are injected with the vaccine only, three injections 30 days apart. The patients are followed for toxicity, the development of anti-PSA immune responses, and evidence of a clinical effect of the vaccination. The latter includes changes in serum PSA and prostatic acid phosphatase (PAP), and the PSA doubling times (PSADT). Patients in protocol #2 also have CT and bone scans to monitor their prostate cancer.

BODY:

The first year of the award, from April 1, 2007 through March 31, 2008, was occupied by negotiations and submissions of documents to the DOD's PCRP, including the Human Subjects Research Review Board (HSRRB), the FDA, NIH's Recombinant DNA Review Committee (RAC), the University of Iowa IRB, the Iowa City VA Medical Center IRB, and the Iowa City VA Medical Center Research and Development Committee. During the second and third years we have been recruiting patients, evaluating their eligibility, screening them for adherence to our entry criteria, vaccinating them and following their clinical and immunological responses according to the schedule described in the protocols.

Recruitment – Patients were initially recruited into the trial from the Urology Clinic in the University of Iowa Hospitals and Clinics (UIHC) and the Urology Service at the adjacent Iowa City VA Medical Center. Additional recruitment was through (1) Referrals from private practice physicians (urologists, medical oncologists, and radiation oncologists) following the mailing of a letter sent to these physicians in the State of Iowa and bordering regions of Nebraska, Missouri, Illinois, Minnesota, and Wisconsin. A follow-up letter to the same physician mailing list was sent in 2009 and a third letter was sent following protocol modifications in 2010. Referrals from academic physicians (urologists, medical oncologists, and radiation oncologists) following a mailing of a letter sent to academic and VA medical centers in the same geographic areas covered by the letters to the private practice physicians. Follow-up letters were sent in 2010. The listing of the trial on www.clinicaltrials.gov website. (2) Presentation of results from the Phase II trial of the Ad/PSA vaccine at the annual meeting of the American Association for Cancer Research (AACR), the American Society of Clinical Oncology (ASCO), the ASCO Genitourinary Malignancies Conference, and the Fall Symposium of the Society for Basic Urologic Research (SBUR), and the North Central Section of the American Urologic Association (AUA). (3) Talks to prostate cancer survivor support groups in at the University of Iowa, Mercy Medical Center in Cedar Rapids, IA, and the Us TOO chapter in Rock Island, IL. (4) Publication in the University of Iowa Hospitals and Clinics' *"Pacemaker"* magazine with a "Q & A" with me about the trial. (5) Publication of the trial in the University of Iowa Hospitals and Clinics' *"UI Consult."* This is a communication that is mailed to all physicians on a very large mailing list. The publication reaches a larger group of physicians than did our list for the letters, particularly family practice and general practice physicians. (6) Publication of the trial in the University of Iowa Hospitals and Clinics' *"Medicine"* magazine. The PI was interviewed and

photographed for the article. Other participants in the article are the Co-PI of the award Dr. Richard Williams and one of our trial patients. (7) Publication in the Department of Veterans Affairs "*VA Currents,"* that is sent via the internet and hard copy to VA Medical Centers.

In the current year we screened a total of 100 patients for their eligibility to enter the trial, but only 9 patients were enrolled (9%). We have modified our protocols to allow more patients to become eligible based upon the new entry criteria.

Enrollment - After all approvals were obtained patients enrolled during the current year are listed in Table 1.

Table
Patients Enrolled from April 1, 2009 to March 31, 2010

Patient ID	Protocol	Arm	Information
APIIAHN-03	1	A	Received all 3 vaccinations and completed visits to 12 months.
APIIAHN-04	1	A	Received all 3 vaccinations and completed visits to 12 months.
APIIAHN-05	1	A	Received all 3 vaccinations and completed visits to 9 months.
APIIAHN-06	1	A	Received all 3 vaccinations and completed visits to 6 months.
APIIAHN-07	1	A	Received all 3 vaccinations and completed visits to 6 months.
APIIAHN-08	1	A	Received all 3 vaccinations and completed visits to 90 days.
APIIAADT-04	1	B	Received all 3 vaccinations and completed visits to 12 months.
APIIAADT-05	1	B	Received all 3 vaccinations and completed visits to 9 months.
APIIB-11	2	---	Received all 3 vaccinations and completed visits to 12 months.
APIIB-11	2	---	Received all 3 vaccinations and completed visits to 12 months.

Adverse Events – During the period of report there were few vaccine-related adverse events (AE), all of them grade 1. Table 2 documents these vaccine-related AE.

Table 2
Vaccine-Related Adverse Events

Protocol #1; Arm A – Hormone Naïve Patients

Patient	Event	Grade	Vaccine Related
APIIAHN-04	Injection site reaction	1	Probable

No vaccine-related adverse events in the other Arm A patient. Total patients = 6

Protocol #1; Arm B – Androgen Deprivation Patients

No vaccine-related adverse events in any Arm B patients. Total patients = 2

Protocol #2; Hormone Refractory Patients

No vaccine-related adverse events in Protocol #2 patient. Total patients = 1

Table 3 lists all of the adverse events documented for each of the currently enrolled patients whether they were deemed vaccine-related or not. The decisions on vaccine relatedness were made by the clinical team, consisting of the clinicians and our clinical trial coordinator.

Table 3
All Adverse Events

Protocol #1; Arm A – Hormone Naïve Patients

Patient	Event	Grade	Vaccine Related
APIIAHN-03	Folliculitis	1	Unlikely
APIIAHN-04	Injection site reaction	1	Probable
	Mucositis-oral	1	Unrelated
	Pain –GI-oral cavity	1	Unrelated
	Infection-other-sinus	2	Unrelated
APIIAHN-07	Fatigue (to 30 days)	1	Unrelated

Protocol #1; Arm B – Androgen Deprivation Patients

Patient	Event	Grade	Vaccine Related
APIIAADT-04	Difficulty sleeping	1	Unlikely
	Increased urinary freq.	2	Unrelated
	Increased urinary urgency	2	Unrelated
	Decreased libido	1	Unrelated
	Increased erectile dysfunct.	2	Unrelated
	Hot flashes	1	Unrelated
APIIAADT-05	Myositis -neck	1	Unrelated
	Gynecomastia	2	Unrelated
	Hot flashes	1	Unrelated
	Mucositis - oral	1	Unrelated

Protocol #2; Hormone Refractory Patients

Patient	Event	Grade	Vaccine Related
No adverse events in Protocol #2 patient.			

KEY RESEARCH ACCOMPLISHMENTS:

For each patient we collected serum for future measurements of anti-PSA and anti-adenovirus antibodies, isolated lymphocytes from the peripheral blood for the measurement of anti-PSA and anti-adenovirus T cell responses, and measured serum levels of PSA and PAP.

PSA Doubling Times (PSADT) – One of the measurements used to follow the clinical pattern of prostate cancer before and after therapy is the change in doubling time of the serum PSA levels. We have evaluated the PSADT of some of the patients in the tria, but have not done so for patients in this grant year due to a change in laboratory personnel. The data for the patients enrolled in the current year are being collected and PSADT will be calculated and reported in future quarterly and annual reports. Table 4 demonstrates that of the nine patients, on whom we had sufficient data to calculate both pre-vaccination and post-vaccination PSADT values, six or 67%, had an increase and three or 33% had a decrease in the values.

Table 4
PSA Doubling Times (PSADT)

Patient	PSADT		Percent Change
	Pre-Vaccination	Post-Vaccination	
APIIAHN-01	26.7 months	20.9 months	-21.7%
APIIAHN-02	14.7 months	48.9 months	+232.7%
APIIB-01	7 months	3.8 months	-45.7%
APIIB-02	9.9 months	11 months	+11.1%
APIIB-04	6.3 months	15.8 months	+150.8%
APIIB-05	17.4 months	11.1 months	-36.2%
APIIB-06	3.1 months	6.1 months	+96.8%
APIIB-07	7.3 months	8.7 months	+19.2%
APIIB-08	5.2 months	10 months	+92.3%
Overall as of 6/25/09 – 6/9 patients (67%) demonstrated an increase in PSADT and 3/9 patients (33%) demonstrated a decrease in PSADT.			

ELISPOT Analysis of Anti-PSA T Lymphocytes Immune Responses – Since the primary arm of the immune response to tumor associated antigens has been documented as the T cell-mediated response, we examined the development of the responses over time after the initiation of vaccination. At each patient visit we obtained peripheral blood and isolated the lymphocytes by density gradient centrifugation. The majority of the lymphocytes were suspended in a cryopreservative solution and stored in liquid nitrogen for future analyses. At the end of the first 12 months following the initiation of therapy all of the samples for each patient will be thawed and an ELISPOT assay performed at one time. This is done to avoid inter-assay variability and will allow us to accurately compare the responses at each time point. When the lymphocyte yields were large such that we were able to cryopreserve sufficient numbers of cells for that single assay and have extra cells, we performed the ELISPOT assays on the freshly isolated cells. This is permitting us to obtain some preliminary measure of the anti-PSA T cells responses for the patients at the appropriate time points. However, the more definitive assays will be those performed on the stored cells after the 12 month time point. In the first year we did not do the 12 month assays, but report here the results of assays performed on patient samples when sufficient cells were available. Again, because of a change in laboratory personnel, ELISPOT data are not available for the patients enrolled in the current year. They are being analyzed and will be presented in future quarterly and annual reports. Table 4 provides the data for the patients previously analyzed. For the patients in protocol #1, Arm A, 2/2 (100%) developed positive anti-PSA T cell responses. For patients in protocol #1, Arm B, 2/2 (100%) developed positive anti-PSA T cell responses. For patients in protocol #2, 3/6 (50%) developed strong responses and 2/6 (33%) developed modest responses. For all patients in this protocol 5/6 (83%) developed positive anti-PSA T cells responses. For all patients in both protocols, 90% developed some level of anti-PSA T cell responses, with 70% developing strong responses.

Table 5
Ad/PSA Phase II Clinical Trial
ELISPOT Analysis of T Cell Responses

Patient	T Cell Frequency		Response
	Pre-Vaccination	Post-Vaccination	
APIIAHN-01	1/2X10E6	1/24,096	+
APIIAHN-02	1/33,000	1/12,000	+
APAADT-01	1/500,000	1/10,050	+
APAADT-02	1/46,512	1/7,463	+
APIIB-01	1/11,426	1/4,357	-
APIIB-02	1/1x10E8	1/10,870	+
APIIB-04	1/500,000	1/8,511	+
APIIB-05	1/130,000	1/2,850	+
APIIB-06	1/154,000	1/51,300	+/-
APIIB-07	1/133,000	1/64,500	+/-

REPORTABLE OUTCOMES:

Presentation of results from the Phase II trial of the Ad/PSA vaccine at the annual meeting of the American Association for Cancer Research (AACR), the American Society of Clinical Oncology (ASCO), the ASCO Genitourinary Malignancies Conference, and the Fall Symposium of the Society for Basic Urologic Research (SBUR), and the North Central Section of the American Urologic Association (AUA).

CONCLUSION:

Patients were enrolled in both protocols, vaccinated three times and followed by return visits to the University of Iowa Hospitals and Clinics and Iowa City VA Medical Center. No serious vaccine-related adverse events were reported for any of the patients. In the analysis of serum PSA and immune responses to PSA following the vaccinations, 67% of the patients demonstrated an increase in PSADT and 90% developed some level of anti-PSA T cell responses, with 70% developing strong responses.

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